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DEVELOPMENT OF A SYNTHETIC BURN COVERING. (U)
JAN 77 J B GREGORY, J D GRESSER, D L WISE
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DEVELOPMENT OF A SYNTHETIC BURN COVERING

Fourth Annual Report

Period: January 1, 1976 to December 31, 1976

Dynatech Report No. 1571

Sponsored by the Office of Naval Research

Contract Authority N00014-73-C-0201

Task No. NK 105-702/11-26-75

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the United States Government

Prepared by:

J.B. Gregory

J.D. Gresser

D.L. Wise

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MAR 30 1977
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Prepared for:

Director, Medicine and Dentistry Programs
Biological and Medical Sciences Division
Office of Naval Research
Department of the Navy
800 North Quincy Street
Arlington, Virginia 22217

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Date Submitted:

January 31, 1977

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DYNATECH R/D COMPANY
A Division of Dynatech Corporation
99 Erie Street
Cambridge, Massachusetts 02139

Telephone: (617) 868-8050

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An evapometer for use directly over the burned area has been designed and is being calibrated. This will permit measuring IWL by resistance hygrometry.

Preliminary experiments have been carried out with ³H-labelled proline to quantitatively measure tissue growth under treated and untreated burns.

Synthetic temporary skin grafts made from PCL film laminated to PCL fabric velours with five different pile depths have been successfully evaluated in vivo using rats. All PCL fabrics and PCL films have been made from high molecular weight polymers synthesized at Dynatech using a special biocompatible catalyst (diethyl zinc). Additional PCL fabric similar to the best of the above has been processed. In addition, a second fabric, a cut plush with greater flexibility, has been knitted. Because the pile in this fabric is individual fibers rather than loops, the damage to underlying tissue when the graft is removed should be eliminated with the new fabric. Further testing of PCL film/PCL fabric laminates is planned to obtain grafts with superior conformance to highly curved surfaces. A manuscript covering earlier work has been accepted for publication in the Journal of Biomedical Materials Research.

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TABLE OF CONTENTS

<u>Section</u>	<u>Topic</u>	<u>Page</u>
	LIST OF TABLES	v
	LIST OF FIGURES	vi
	LIST OF PLATES	vi
	REFERENCES	vii
1	SUMMARY	1
2	INTRODUCTION	3
3	DEVELOPMENT OF SOLUTIONS FOR IMMEDIATE POST-BURN TREATMENT	6
3.1	Introduction	6
3.2	Initial <u>In Vivo</u> Evaluations	6
3.2.1	Methods	7
3.2.2	Results and Discussion	7
3.3	Further <u>In Vivo</u> Tests Using Penthane As the Anesthetic	11
3.3.1	Methods	11
3.3.1.1	The Burn Model	11
3.3.1.2	The Abrasion Model	11
3.3.1.3	Photography	12
3.3.2	Results	12
3.3.3	Discussion	
3.4	Study of Plasticized PCL Films	19
3.5	Development of Techniques for Using Labelled Proline for Quantitative Measure of Tissue Growth by Traumatized Rats	22
3.6	Resistance Hygrometry	24
3.6.1	Measuring Potential Uptake of PCL When Applied Topically	26
3.6.2	Using ^3H -labelled Proline for Quantitative Measure of Scar Formation	26

TABLE OF CONTENTS (continued)

<u>Section</u>	<u>Topic</u>	<u>Page</u>
	3.6.3 Application of PCL Solutions	26
	3.6.4 Plasticizing PCL	26
4	SYNTHETIC GRAFT	27
4.1	Polymerization	27
4.2	Melt Spinning	30
4.3	Knitting	36
4.4	Lamination of PCL Fabric to PCL Film	37
4.5	<u>In Vivo</u> Evaluation	37
4.6	Further Work on the Development of PCL Fabric Film Laminate Burn Coverings	39
4.6.1	Complete Preparation of Selected Fabrics Fabrics for Lamination	40
4.6.2	Evaluation of Fabric/Laminate Burn Covering	40
4.6.3	Supply Samples and Coordinate Work with NMRI	40
4.6.4	Evaluation of Burn Covering Materials in Anticipation of Clinical Trials	40
APPENDICES TO SECTION 4		
4.1	Polymerization of 6-Hexanolactone (ϵ -Caprolactone) to Poly- ϵ -Caprolactone	41
4.2	Preparation of PCL Fiber Lot 2 Melt Spun by SRI	43
4.3	Preparation of PCL Fiber Lot 3 Melt Spun by SRI	47
4.4	Preparation of PCL Fabric/PCL Film Laminates	51
4.5	Description of the Burned Rat Model Excision and Grafting Procedures	53
APPENDIX A		
U.S. Patent #3,935,308 (Jan. 27, 1976), Wound Covering and Method of Application		55

LIST OF TABLES

<u>Table</u>		<u>Page</u>
2.1	Desirable Characteristics of Synthetic Skin Substitute	5
3.1	Mean 24 Hour Insensible Water Loss Rates (gm/24 hr) from Burned Rats as a Function of Time from Application and Thickness of Film (Pentobarbital Anesthetic)	9
3.2	Mean 24 Hour Insensible Water Loss (gm/24 hr) from Rats as a Function of Skin Condition and Anesthetic	10
3.3	Mean Insensible 24 Hr Water Loss in Gms at Various Times Post Burning	14
3.4	Mean Weight of Animals During Experiment	14
3.5	Mean 24 Hr Insensible Water Loss for Abrasion and Control Experiments	15
3.6	Mean Weight Loss During Abrasion and Control Experiments	16
3.7	Thickness of Burn Covering Layer in Each Group of Animals	17
3.8	Study of Plasticized Films	21
3.9	Uptake of ^3H Proline by Traumatized Rats	23
4.1	Summary of ϵ -Caprolactone Polymerizations	29

LIST OF FIGURES

<u>Figure</u>		<u>Page</u>
3.1	Wipe-on Covering Test, Abrasion Model	18
3.2	Wipe-on Covering Test, Alcohol Burn Model	20

LIST OF PLATES

3.1	Procedure for Weighing Animals	13
3.2	Burned Animal with No Covering at 48 hrs.	13
3.3	Abraded Animal with No Covering at Day 8	13
3.4	Burned Animal with 1 mil Covering at Day 8 after Removal of Covering	13
3.5	Evapometer Used to Measure Water Loss from Skin of Arm	25
4.1	Large Scale Polymerization of Distilled 6-hexano-lactone to Poly- ϵ -caprolactone	28
4.2	Precipitation of Poly- ϵ -caprolactone in hexane.	28
4.3	Poly- ϵ -caprolactone Coming out of 68 Orifice Spinneret and Passing through Air Quench Chamber	32
4.4	The yarn is drawn as it passes from a Feed Godet over a Heated Platen to a Second Godet Operating at a Higher Speed than the First	35
4.5	Front View of Raschel Double Bar Knitting Machine.	38

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Section 1

SUMMARY

Work during the past year with rats has confirmed the reduction of insensible water loss (IWL) from full thickness burned areas when coated by a solution of poly- ϵ -caprolactone (PCL) which leaves a dry film about 1 mil thick. Long lasting anesthetics used in the first in vivo tests reduced metabolism, thus somewhat masking this effect, but recent experiments using Penthrane, a short-term anesthetic, confirmed the benefit of the coating during the first 24 hours. Sufficient amounts of this wipe-on material have been prepared for testing by NMRI on a large number of swine. U.S. Patent #3,935,308 was granted to the U.S. Navy on this "wound covering and method of application." (See Appendix A)

An evapometer for use directly over the burned area has been designed and is being calibrated. This will permit measuring IWL by resistance hygrometry.

Preliminary experiments have been carried out with ^3H -labelled proline to quantitatively measure tissue growth under treated and untreated burns.

Synthetic temporary skin grafts made from PCL film laminated to PCL fabric velours with five different pile depths have been successfully evaluated in vivo using rats. All PCL fabrics and PCL films have been made from high molecular weight polymers synthesized at Dynatech using a special biocompatible catalyst (diethyl zinc). Additional PCL fabric similar to the best of the above has been processed. In addition, a second fabric, a cut plush with greater flexibility, has been knitted. Because the pile in this fabric is individual fibers rather than loops, the damage to underlying tissue when the graft is removed should be eliminated with the new fabric. Further testing of PCL film/PCL fabric

laminates is planned to obtain grafts with superior conformance to highly curved surfaces. A manuscript covering earlier work has been accepted for publication in the Journal of Biomedical Materials Research.

Section 2

INTRODUCTION

The prompt treatment of major flesh burns to reduce shock and trauma caused by shipboard fire and explosions are of prime interest to the Office of Naval Research. The inability of burned skin to function as an effective barrier to evaporative water loss and sepsis contributes significantly to the mortality resulting from major burns. It has been shown that the average evaporative water loss for patients whose second- and third-degree burns ranged from 18 to 40 percent of the body surface is 3260 ml/29 hrs for a 50 percent burn (Reference 1). This loss requires an energy expenditure of 1891 calories to maintain temperature, and to counteract this depletion, metabolic reserves are mobilized and muscle protein and fat losses occur unless heat is supplied artificially. In the short run, this process can result in shock. In the long run, any such losses contribute to the debility of the patient, delay wound healing, and increase the susceptibility of the patient to disease.

The objective of the program covered by contract no. N00014-73-C-0201 is the development of a synthetic polymer burn covering which will reduce dehydration, sepsis, sodium loss, scar formation and mortality in burn patients. The target material is to be producible at low-cost and in large quantities so as to be immediately available in event of large-scale disasters.

From the inception of the program on February 1, 1973, work has been concentrated on two approaches. First, the development of a solution of a plastic that can be applied immediately after the burn by wiping or spraying it onto the burned area. After evaporation of the solvent, the protective film left is expected to limit water loss from the burned area and reduce the trauma from the burn. The second approach is the development of a burn covering to be applied to the burned area after debridement and excision of the burned tissue. This coating which will be of a temporary nature should prevent dessication and promote the formation in the under-

lying wound bed of a viable, well-vasculated interface free of sepsis which will be suitable for the application of skin grafts taken from other areas of the patient's body.

Human and porcine skin have been successfully used in the treatment of major skin wounds which result from second and third degree burns. There are, however, major problems with availability, expense and handling. As a result, those such as the U.S. Navy confronted with the possibility of a mass casualty are well aware of the need for a synthetic burn covering that is easily manufactured and can be stored for long periods without references to frozen storage or other specialized methods. (References 2, 3, 4)

Many materials and composites have been tried -- polyurethane foam laminated to polypeptide or silicone films, collagen, and polyvinyl-alcohol. A variety of forms -- foams, film, velours, and sponge -- have been investigated. (References 5, 6, 7, 8) At the present time, there is no satisfactory replacement for natural skin, human or porcine, in the treatment of major skin wounds.

The desirable characteristics of any synthetic covering are listed in Table 2.1

Section 3 covers the discussion of the development of a solution of plastic for wiping or spraying onto the burned area immediately after the accident, and Section 4 describes the development of the synthetic coating which is to be applied later after the burned area has been debrided and excised as required.

Table 2.1

DESIRABLE CHARACTERISTICS OF SYNTHETIC
SKIN SUBSTITUTE
(Reference 9)

Nonantigenic
Nontoxic to viable tissue
Exclude exogenous bacteria
Thin, pliable, and elastic, but resistant to linear
and shear stress
Semipermeable to H_2O vapor
Rapidly adherent
Porous undersurface with firm intimate bonding to
wound
Prevent bacterial proliferation and promote
bacterial reduction at wound interface
Inexpensive with indefinite shelf life and minimal
storage requirements

Section 3

DEVELOPMENT OF SOLUTIONS FOR IMMEDIATE POST-BURN TREATMENT

3.1 Introduction

During the first year of this program which is now beginning its fifth year, it was found that a 20% solution of poly- ϵ -caprolactone (PCL) in tetrahydrofuran, when wiped onto burns on rats, significantly reduced insensible water loss for up to 10 days and had good adherence. Films made by applying two or more coats adhered less well than those made by applying only a single coat.

During the second year, more extensive work with this wipe-on system showed that the PCL film hardened and did not conform well to the back and its movements. Some of the solution was packaged in an aerosol container so the film could be applied to the burned area by spraying rather than by swabbing or brushing.

During the third year of the project, work was concentrated on the development of a synthetic covering to be applied to debrided and excised wounds, and no work was done on the solutions for immediate post-burn treatment.

During the past year covered by this fourth annual report, additional rat tests of the wipe-on covering have been performed (SISA, Incorporated) in preparation for extensive evaluation on patch-burned pigs.

3.2 Initial In Vivo Evaluations

The procedure used for the first two series of tests performed during the period covered by this report and the discussion of the results follow.

3.2.1 Methods

Male albino Wistar rats were anesthetized with an intraperitoneal injection of sodium pentobarbital (50 mg/kg) or by exposing them to an atmosphere containing Penthane vapor. The backs of the animals were shaved and, in the cases of the animals to be burned, the excess fur was removed using a depilatory (Nair). A template (20 cm²) was placed on the back of the animal and 1.5 ml of ethyl alcohol was instilled into the template. Ignition was followed by an approximately 45-second burn.

Fifteen minutes following the burning, poly- ϵ -caprolactone was applied to the burn by brushing on a 10% solution in acetone/methylene chloride. In one experiment, three thicknesses of PCL were evaluated. The three thicknesses were attained by several applications of the same polymer solution. For example:

Group	No. of Animals in Group	# Applications	Mean Thickness (Inch)
1	6	1	0.00049 ± 0.00005
2	9	2	0.00012 ± 0.0003
3	7	3	0.0024 ± 0.00012

The mean insensible water loss was determined at 4, 8, 12, 24, 28, 32 and 36 hours post-application and then at two-day intervals until day 10. The insensible water loss was determined by weighing each animal in a small acrylic restraining cage every ten minutes for a period of thirty minutes. The results were corrected for increased growth.

3.2.2 Results and Discussion

Two sets of experiments were performed: the first to characterize the effects and behaviors of three thicknesses of PCL film on the alcohol burns; and the second to clarify certain results of the first experiment.

The data for the mean insensible water loss from three groups of animals, each with wounds covered with one of the above thicknesses of PCL

film, are presented in Table 3.1. Initially the insensible water loss (IWL) rates were well below the control values (11-12 gm/24 hr.). However, the observation was made that the activity of the animals was also depressed during the early post-burn treatment as the animals recovered from anesthesia. (See below)

The best control of IWL was realized in those animals whose covering -- regardless of thickness -- remained intact. The 0.001" coverings were the most successful as 90% of the coverings remained on the animals for the full ten days. The 0.0005" coverings were too thin and easily flaked off. The 0.002" coverings were too thick and lacked the conformability to stay on the rat's back. The thickest coverings broke away from the wounds at the edges and the animals further aggravated the situation by chewing at their wounds.

To test whether or not the anesthetic affects the IWL's during the immediate post-burn period, a second series of tests were performed to compare the IWL's of animals anesthetized with sodium pentobarbital with that of animals anesthetized with Penthane. Both are general anesthetics, but the effect from exposure to Penthane vapor is more quickly dissipated and, therefore, the effect of the anesthetic on early post-burn IWL's could be characterized by the comparison.

The IWL's of pentobarbital-anesthetized animals; burned but not covered, burned and covered, and only shaved are compared with those of animals shaved while under Penthane anesthetic and are presented in Table 3.2. Especially telling are the data through 24 hours in columns 4 and 5 of the table. IWL's of shaved animals anesthetized with Penthane were at normal levels until sometime between 12 and 24 hours. Evidently the type of anesthetic used in this type of experiment has a significant effect on the early post-burn results, casting doubt on previously obtained data -- particularly the drastic reductions in IWL's immediately post-burn.

Table 3.1

MEAN 24 HOUR INSENSIBLE WATER LOSS RATES (gm/24 hour)
 FROM BURNED RATS AS A FUNCTION OF TIME FROM APPLICATION AND THICKNESS OF FILM
 (Pentobarbital Anesthetic)

Time	Rate (gm/24 hr)					
	Covering Thickness (inch)					
	N*	0.0005	N*	0.001	N*	0.002
4 hr	9	9.07 ± 1.43	10	9.84 ± 2.21	10	8.88 ± 1.20
8 hr	9	8.27 ± 0.99	10	9.36 ± 1.28	10	9.84 ± 0.98
12 hr	9	20.0 ± 3.44	10	16.08 ± 3.27	9	13.87 ± 2.52
24 hr	5	14.88 ± 1.12	9	15.73 ± 3.17	5	16.32 ± 2.44
28 hr	5	13.44 ± 1.62	9	11.70 ± 1.20	5	14.40 ± 2.00
32 hr	5	13.92 ± 0.90	9	13.33 ± 1.55	5	8.64 ± 2.22
36 hr	5	8.64 ± 0.59	9	13.12 ± 2.18	5	11.52 ± 1.17
Day 4	5	17.76 ± 2.09	9	20.80 ± 1.70	5	21.12 ± 1.40
Day 6	5	17.79 ± 2.22	9	14.93 ± 1.48	5	17.76 ± 1.22
Day 8	5	20.64 ± 3.09	8	14.70 ± 1.47	5	20.16 ± 2.22
Day 10	5	19.68 ± 1.40	9	18.13 ± 1.65	5	20.64 ± 2.22

N* = number of animals surviving in each group

Table 3.2

MEAN 24 HOUR INSENSIBLE WATER LOSS (gm/24 hr) FROM RATS
 AS A FUNCTION OF SKIN CONDITION AND ANESTHETIC
 FIGURES IN PARENTHESES ARE THE NUMBER OF ANIMALS TESTED

Time	Burned Animals		Shaved Animals	
	No Covering	1.0 mil Covering	Pentobarbital	Anesthetic
4 hr	6.80 ± 0.74 (6)	5.20 ± 0.40 (6)	6.24 ± 0.59 (6)	12.40 ± 1.15 (6)
8 hr	6.40 ± 0.80 (6)	6.84 ± 1.30 (6)	7.20 ± 0.76 (6)	10.81 ± 0.54 (6)
12 hr	5.84 ± 0.55 (6)	5.63 ± 0.51 (6)	5.76 ± 0.59 (6)	—
24 hr	10.44 ± 1.72 (6)	6.20 ± 2.11 (6)	11.04 ± 1.62 (6)	11.57 ± 1.44 (6)
28 hr	15.79 ± 2.02 (6)	10.84 ± 0.82 (3)	13.44 ± 1.63 (6)	11.22 ± 1.60 (6)
32 hr	12.11 ± 1.07 (5)	*14.33 (2)	11.21 ± 1.04 (6)	10.88 ± 1.51 (6)
36 hr	14.38 ± 1.31 (5)	*15.71 (2)	12.48 ± 0.48 (6)	—
Day 4	16.83 ± 1.79 (5)	*13.84 (2)	13.01 ± 0.71 (6)	9.63 ± 0.88 (6)
Day 7	17.44 ± 2.2 (4)	—	11.62 ± 0.41 (6)	10.64 ± 1.17 (6)

*Survivors' covering was not intact.

3.3 Further In Vivo Tests Using Penthane As the Anesthetic

Since it had been shown that long-lasting anesthetics such as pentobarbital may have invalidated the effect of the wipe-on coating on IWL, a new series of animal tests was initiated at SISA, Inc. These experiments differ from those previous in several important ways as follows.

- (a) New restraining cages were used. These were built of 1/2-inch screening material and measured 6 x 2 1/2 x 2 1/2.
- (b) All experiments were performed using Penthane in place of pentobarbital.
- (c) In addition, a new model for a wound -- the abrasion model -- was tested.

3.3.1 Methods

3.3.1.1 The Burn Model

Male Wistar rats (200-240 g) were anesthetized, shaved and burned as described in 3.2.1 except that no depilatory was used. The insensible water loss was determined for two groups of 10 animals, one burned and covered with a 1.0 mil film of PCL covering applied as described in section 3.2.1, and the other burned, but not covered, at 3 hr, 6 hr, 27 hr, 30 hr, 54 hr, 78 hr and 150 hr. The data were corrected for changes in the weight of the animals due to normal growth.

3.3.1.2 The Abrasion Model

Twenty male Wistar rats (200-240 g) were anesthetized and shaved. Ten animals were abraded with a 3" diameter wire brush connected to a drill operated at 2100 r.p.m. 5 of these animals were treated as controls and the other five were covered with 1.0 mil of the PCL covering. Of the remaining 10 animals, 5 were coated with 1.0 mil of the PCL covering and

the other 5 were untreated. Insensible water loss was determined at 3 hr, 6 hr, 27 hr, 30 hr, 54 hr, 78 and 102 hr. All data were corrected for weight changes during the experiment.

3.3.1.3 Photography

All experiments were photographed using 35 mm film for making slides. The most significant have been enlarged and are included in this report as Plates 3.1 to 3.4.

3.3.2 Results

The average 24 hour insensible water loss from the burn experiment corrected for weight are presented in Table 3.3. The weight changes over the 7-day period are presented in Table 3.4.

The abrasion experiment data are presented in Tables 3.5 and 3.6.

The film thicknesses were measured at the end of each experiment and are recorded in Table 3.7.

3.3.3 Discussion

The use of Penthrane in place of pentobarbital has proven an advantage for monitoring insensible water loss during the early time periods post burning. Furthermore, the use of wire restraining cages (see Plate 3.1) in place of the acrylic cages used previously is more satisfactory since water does not condense on the wire.

The burn coverings significantly reduce IWL in the burn experiment at the early time intervals (see Figure 3.1). By 30 hours, the burned animals with the covering had started to bite at their wounds and a strict comparison of the two groups was not valid (see Plate 3.2). By 54 hours, four out of ten animals in this group had significant open wounds on their bodies, whereas the non-covered group showed no wounds. By 78 hours, all of the covered group showed severe deterioration of the burn cover, whereas

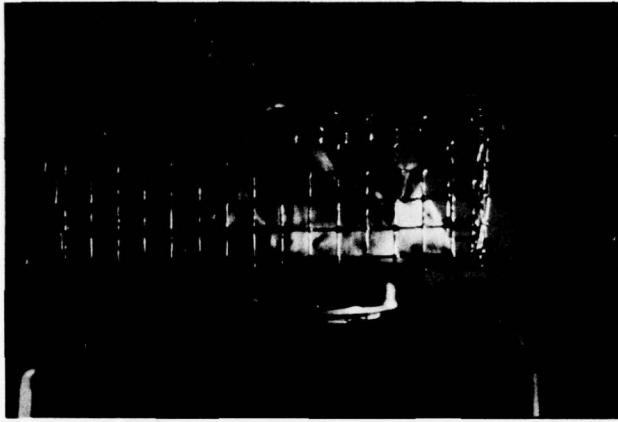


Plate 3.1. Procedure for Weighing Animals



Plate 3.2. Burned Animal with No Covering at 48 hrs.



Plate 3.3. Abraded Animal with No Covering at Day 8



Plate 3.4. Burned Animal with 1 mil Covering at Day 8 after removal of covering

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Table 3.3

Mean insensible 24 hr water loss in gms at various times post burning

Group description	TIME POST BURNING						
	3 hr	6 hr	27 hr	30 hr	54 hr	78 hr	150 hr
Burned and covered	10.32	10.16	13.57	19.15	20.40	22.67	28.81
	±0.62	±0.92	±0.95	±0.87	±1.86	±1.38	±2.12
Burned but not covered	13.68	19.19	17.52	14.69	16.76	21.98	21.06
	±0.72	±1.26	±1.52	±1.03	±1.03	±2.53	±1.40

Table 3.4

Mean weight of animals during experiment.

Group description	TIME POST BURNING						
	3 hr	6 hr	27 hr	30 hr	54 hr	78 hr	150 hr
Burned and covered with 1.0 mil covering	239.1	237.2	228.4	224.8	227.8	225.3	243.7
	±5.8	±5.8	±5.9	±5.9	±5.5	±5.7	±5.5
Burned but not covered	222.7	222.0	210.5	207.4	207.3	206.7	220.8
	±4.6	±4.4	±6.0	±5.7	±7.3	±7.3	±7.0

Table 3.5

Mean 24 hr insensible water loss for abrasion and control experiments.

Group description	TIME POST ABRASION						
	3 hr	6 hr	27 hr	30 hr	54 hr	78 hr	
Abraded - covered	27.36 ±1.20	25.95 ±1.92	22.74 ±2.90	24.97 ±1.47	23.09 ±1.47	20.04 ±2.01	20.89 ±2.41
Abraded - but not covered	35.04 ±0.58	37.89 ±1.42	32.55 ±1.07	30.63 ±1.98	29.02 ±0.50	21.96 ±1.46	19.89 ±0.49
Shaved - covered	12.00 ±1.54	11.03 ±1.44	8.73 ±0.48	10.26 ±0.98	14.34 ±0.96	11.97 ±0.92	14.11 ±0.94
Shaved - but not covered	14.88 ±1.40	13.85 ±0.96	13.23 ±0.48	9.38 ±1.48	17.75 ±1.97	11.83 ±0.93	12.01 ±1.44

Table 3.6

Mean weight loss during abrasion and control experiments.

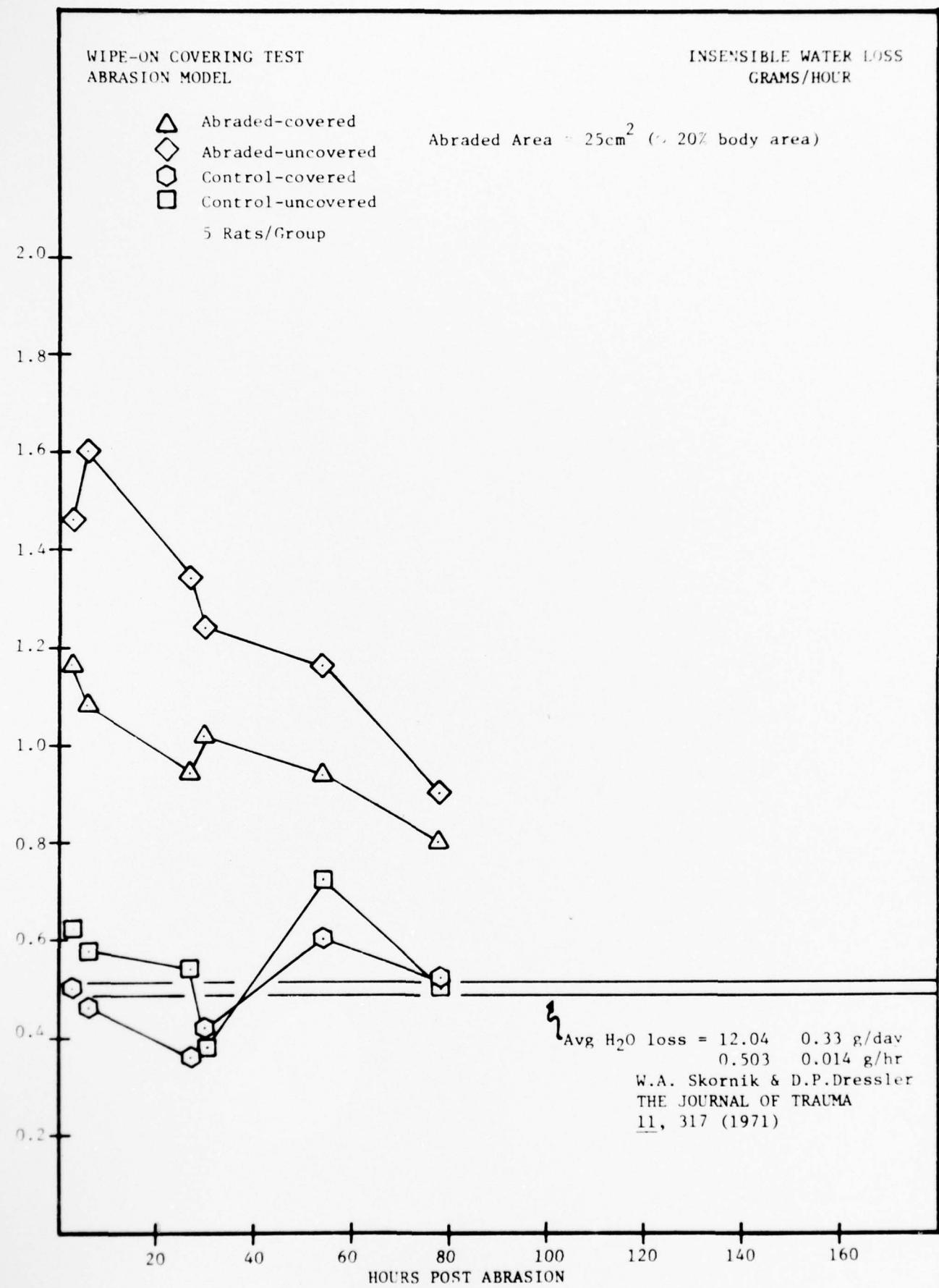
Group description	TIME POST ABRASION						
	3 hr	6 hr	27 hr	30 hr	54 hr	78 hr	
Abraded - covered	197.7 ±3.8	197.5 ±3.8	196.1 ±4.0	193.8 ±4.0	193.2 ±2.0	189.4 ±5.1	195.3 ±3.5
Abraded - but not covered	208.7 ±2.7	211.5 ±3.7	206.2 ±3.0	202.8 ±2.6	200.2 ±4.8	205.3 ±4.2	206.5 ±3.9
Shaved - covered	206.5 ±5.2	206.7 ±5.9	204.4 ±5.3	202.8 ±5.1	207.3 ±5.5	215.3 ±4.9	210.7 ±3.7
Shaved - but not covered	210.8 ±5.0	211.9 ±5.7	206.5 ±4.4	205.0 ±4.5	205.2 ±5.5	213.8 ±5.3	210.6 ±6.2

Table 3.7

Thickness of burn covering layer in each group of animals.

<u>Group</u>	<u>Thickness in inches</u>	<u>No. of Animals Tested</u>
Burned	0.0014± 0.00012	9
Abraded	0.0008± 0.00017	5
Control	0.0009± 0.00036	3

FIGURE 3.1



only two in the non-covered had open wounds. By 150 hours one of the covered animals was dead and all others had severe wounds. Four out of ten of the uncovered animals had open wounds. The conclusion is that the burn covering had a significantly reduced water loss during the first 27-30 hours, but was sufficiently irritating to the rats to cause them to bite at it. The changes in body weight during this experiment were similar for both groups. Because of the irritation of the covering, work was initiated to determine if suitably plasticized PCL films could be prepared which would be less irritating (see Section 3.4).

In the second series of experiments using the abrasion rat model, there was a significant improvement in the covered group which was apparent during the whole experiment (see Figure 3.2). The abrasion model provided the highest water loss we have seen to date. Furthermore, while there was some deterioration of the burn covering, the animals did not bite at their wounds. Demonstration of the water-retaining properties of the burn covering was thus possible for the entire duration of the experiment (80 hrs).

There were only slight differences in the water loss observed with shaved animals and shaved animals to which the burn covering had been applied. In the uninjured state, the rat loses very little water via the skin so that any differences are masked by the experimental error in the IWL measurement. The control values for the 24-hour insensible water loss are well in line with previously reported figures.

The animals used in the abrasion model were examined for wound healing to day 10. The animals which had been covered showed cleaner and more uniform healing than those that were uncovered (compare plates 3.3 and 3.4).

3.4 Study of Plasticized PCL films

The details of the study of plasticizers for PCL are summarized in Table 3.8. 20 parts by weight of triethyl citrate per hundred parts of resin decreases the modulus of the PCL by about 50% and increases the water

FIGURE 3.2

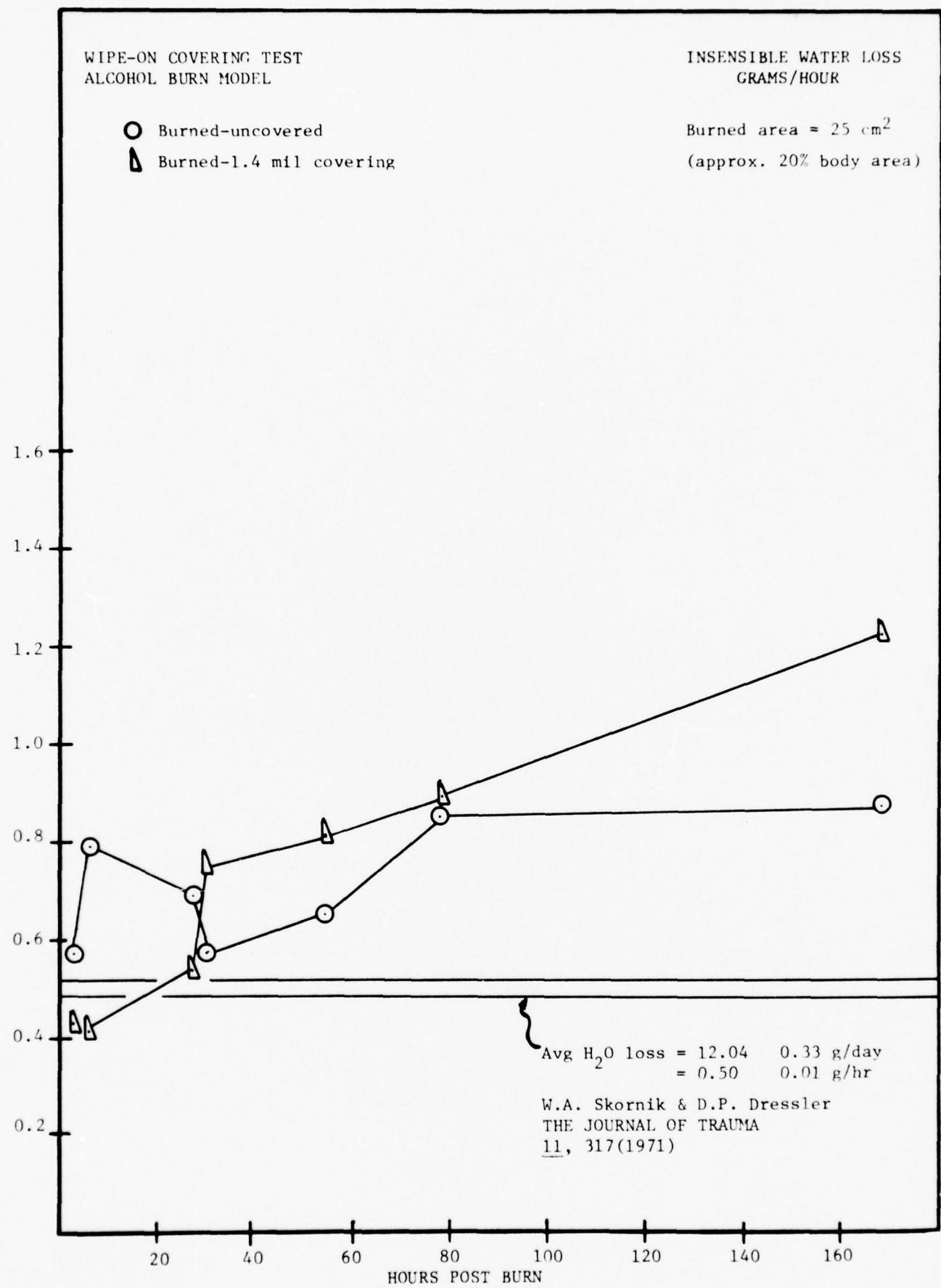


Table 3.8
STUDY OF PLASTICIZED FILMS

PHR Plasticizer by weight (1)	Nature of Plasticizer (2)	Tensile Strength (3) psi	Elongation at Yield (3) %	Young's Modulus (3) psi $\times 10^{-4}$	WVT (4) g/mm ² /24hrs m ²
				g/mm ² /24hrs m ²	
0	—	1120	2	7.5	4.62
5	A	1600 \pm 600	4.2 \pm 2	5.6 \pm 1.1	—
5	B	1820 \pm 540	4.2 \pm 1.2	5.2 \pm 2.3	—
10	A	1940 \pm 650	6.3 \pm 2.3	4.7 \pm 1.1	—
10	B	1700 \pm 690	5.5 \pm 2.0	4.3 \pm 1.7	—
20	A	1690 \pm 170	10.3 \pm 1.4	3.0 \pm 0.1	5.06
20	B	1860 \pm 340	7.8 \pm 2.0	3.6 \pm 0.4	6.62

NOTES

- (1) A basic solution was made up containing 50 grams of PCL polymer 22392, 100 mls of methylene chloride and 400 mls of acetone giving a 10% by weight solution of PCL. This polymer has an approximate molecular weight of 135,000 (see Table 4.1 in the Third Annual Report of this project, submitted January 27, 1976). PHR = Parts by weight per hundred parts of resin.
- (2) The amounts of plasticizer to give the parts by weight indicated of plasticizer based on 100 parts of polymer were added to the base solution. A = triacetin (Eastman Kodak Co.); B = triethyl citrate (Charles Pfizer and Co. Citroflex 2).
- (3) Films of the solution were cast on release paper using a film caster set at 0.025 inches and allowed to air dry and then evacuated for 24 hrs. giving a dry film thickness of about 1 mil. Dumbell samples were cut using Die C specified in ASTM Method D412 and tested for tensile and elongation at yield and Young's modulus using an Instron Tensile Tester Model TTC with a cross-head speed of 0.1 inches per minute.
- (4) Water vapor transmission obtained at 37°C and 0% relative humidity using ASTM Method E96 Procedure D.

vapor transmission by about 50%. Since the tensile strength of the plasticized film at yield is still quite good, films with still higher amounts of plasticizer will be evaluated during the next year of the program.

It should be noted that the water vapor transmission of the un-plasticized PCL film is only about one-quarter that of the value reported in Table 4.1 of the first annual report on this project dated January 31, 1974. However, the respective moduli of the PCL films tested were about 3.6 and 7.5 indicating that the PCL film tested during the first year of the program was of a much lower molecular weight. This would explain much of the difference in water vapor transmission. To duplicate the water vapor transmission of normal human skin, $83 \text{ g} \cdot \text{mm} / 24 \text{ hr} \cdot \text{m}^2$ for an assumed thickness of 0.006" or 150 mm, a plasticized PCL film having a WVT of only $6.62 \text{ g} \cdot \text{mm} / \text{hr} \cdot \text{m}^2$ should be only $\frac{83}{6.62} \approx 12 \text{ mm}$ or about 0.0005" thick. Since making pinhole-free films this thin is rather difficult, further addition of plasticizer and a concomitant increase in the WVT is indicated so that the WVT of human skin can be duplicated with films about 0.001" thick. Such films will also conform better to burned areas and will be less irritating because of their greater flexibility.

3.5 Development of Techniques for Using Labelled Proline for Quantitative Measure of Tissue Growth by Traumatized Rats

The results of this first round of tests (see Table 3.9) do not indicate a greater uptake of proline by traumatized animals. We believe, however, that this may be due to certain inadequacies in experimental design. The changes in procedure suggested by this first experiment are as follows.

- (a) Proline incorporation into tissue may not be complete at four hours. We will repeat this test at 4 hours as well as sacrifice at 8 and 16 hours post injection.
- (b) Our route of administration, IP, may have allowed proline solution to bathe tissues surrounding the peritoneal

Table 3.9
UPTAKE OF ^3H PROLINE BY TRAUMATIZED RATS⁽¹⁾

<u>Group %</u>	<u>Treatment</u>	<u>^3H Found DPM/g</u>
I	Shave, depilate, anesthetize (controls)	5035 3893 <u>1123</u>
	Ave ⁽³⁾	<u>3350 \pm 2011</u>
II	Shave, depilate, anesthetize, burn, cover	2447 1042 <u>1539</u>
		<u>1676 \pm 712</u>
III	Shave, depilate, anesthetize, burn	1069 922 <u>(2)</u>
		<u>996 \pm 104</u>
IV	Shave, depilate, anesthetize, cut, clip	1976 2576 <u>2859</u>
		<u>2470 \pm 451</u>

NOTES

(1) The Wistar rats were depilated by applying Nair cream. After about 5 minutes the cream was removed by sponging with warm water. Ethyl ether was used for the anesthesia. The animals were burned over a 11.9 cm^2 area by applying and igniting 0.75 ml of 200-proof ethanol inside a template held against the side of the rat. The burns on group II were covered by two applications of 26314 which contains 100 grams of poly- ϵ -caprolactone 22392 in 800 mls of acetone and 200 mls of methylene chloride. Previously this has been found to give a dried film thickness of $0.0012" \pm 0.0003"$. All rats were injected after treatment IP with 10 ml of a water solution of $\text{l-}\text{proline}$ [$4-\text{H}(\text{N})$] (New England Nuclear NET-437) having a specific activity of $10\mu\text{Ci}/\text{ml}$. The animals were sacrificed 4 hrs. after injection and a representative sample of the traumatized area removed by cutting through the skin into the peritoneal cavity. This sample was then weighed, oxidized and counted for ^3H .

Group IV was cut through the skin for a distance of about 1" and the skin separated from the layer beneath over a total area of about one square inch. The wound was then clipped together with 9mm stainless steel wound clips.

(2) Rat died shortly after injection.
(3) Mean \pm standard deviation.

cavity. By excising tissue to the peritoneal cavity, tissue samples may have been contaminated with unincorporated proline. Oral administration would circumvent this problem.

(c) Tissue from the burned animals included eschar. As this is dead tissue, no proline could have been incorporated and hence the radioactivity per gram of tissue will accurately reflect proline metabolism only if dead tissue is first eliminated from the sample. The low tritium count in the burned groups reflect this. We have explored methods of excizing and sampling only subdermal tissue without eschar. Thus in subsequent experiments the samples taken will not be diluted with dead tissue and proline metabolism will be more accurately reflected.

3.6 Resistance Hygrometry

The present method for determining insensible water loss is to weigh the animals over a period of thirty minutes, repeating the measurement if the animal voids during the period. This technique for measuring insensible water loss (IWL) is only partially satisfactory when using rats and becomes quite impractical if the experiment is to be scaled up by swine testing. Therefore, an evapometer which will fit over a fixed area of skin has been designed for measuring the moisture loss quantitatively in weight/area by passing a gas through the evapometer and over the skin at a measured rate, using the apparatus which reads out the change in the moisture content of the gas before and after passing through the cup. A similar apparatus has been described by others (Ref. 10 to 14). The evapometer is currently being calibrated at various flow rates by clamping it over cups containing water and covered by membranes of various kinds and measuring the water loss both by weighing the cup of water and a tube of water absorbent through which the exiting gas is passed before and after the test (see Plate 3.5). We plan to obtain a resistance hygrometer sold by Hydrometrics Products, a

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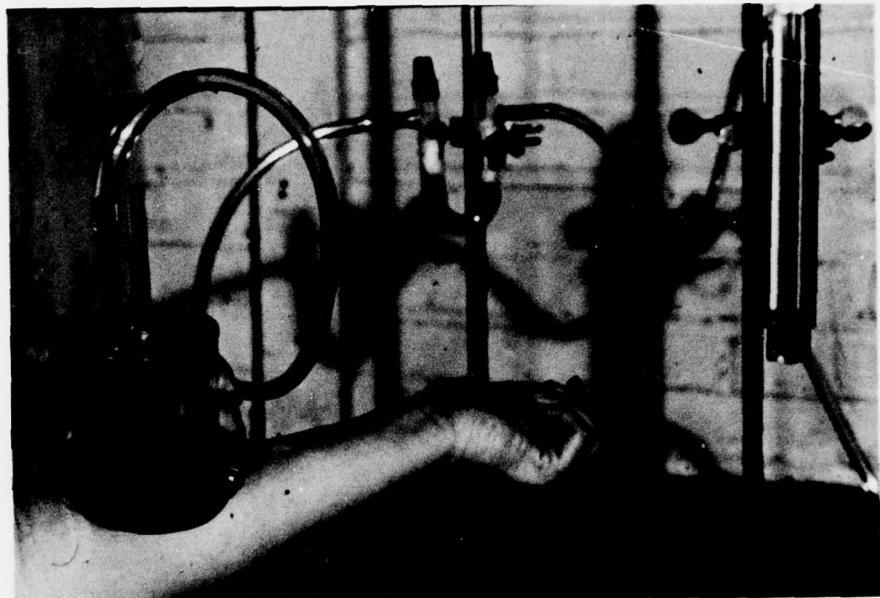


Plate 3.5. Evapometer Used to Measure Water Loss from Skin of Arm.

Division of American Instrument Company, Silver Spring, Maryland, for measuring the moisture content of the air as the use of the tube of absorbent which has to be weighed at periodic intervals in order to calculate the water loss would make the test rather cumbersome for use on swine which are unlikely to remain motionless for prolonged periods needed for measuring the water loss by collecting the water in an absorbent and weighing. These Hygrodynamics resistance hygrometers have been successfully used by Bullard (Reference 11) for measuring sweating rate, using an evapometer designed using the principles used by us.

3.6.1 Measuring Potential Uptake of PCL When Applied Topically

Solutions of ^{14}C -labelled PCL have been prepared. These will be used for immediate post-burn treatment of animals which will then be sacrificed and evaluated for the presence of ^{14}C from the PCL in the tissues by combustion analysis. Information of this kind will be required prior to approval of the materials for clinical trials.

3.6.2 Using ^3H -labelled Proline for Quantitative Measure of Scar Formation

This work is being continued.

3.6.3 Application of PCL Solutions

During the second year of the program, a PCL/THF/acetone solution was packaged in an aerosol container. However, it has been difficult to obtain a smooth film using this aerosol because the solution cools as it is sprayed, causing the solution to gel. Work is planned to find a better solvent system for the PCL which will not cause this difficulty. Secondly, the incorporation of plasticizer should lower the temperature at which the solution gels.

3.6.4 Plasticizing PCL

Work is continuing on plasticized PCL to improve the conformance and water vapor transmission of the PCL film formed when the PCL solvent solution dries.

Section 4

SYNTHETIC GRAFT

The characteristics desirable for synthetic graft have been enumerated in early reports and include a surface, which when placed onto a wound resulting from removal of burn eschar, promotes the adherence of the graft to the wound. Velours, non-woven fiber mats, and foams are examples of such a surface. A second component of the covering is a membrane (film) which controls evaporative water loss from the wound. Engineers at Dynatech have proposed that both the adhering surface and the membrane be prepared from the same polymer, poly- ϵ -caprolactone (PCL).

Good films have readily been prepared using PCL's having intrinsic viscosities in benzene at 37°C of over one. The descriptions of the polymerization, spinning, and knitting steps, which were taken this year towards the fabrication of a synthetic graft, follow.

4.1 Polymerization

In order to prepare enough PCL for spinning and knitting, several batches have been prepared in a 22 liter reaction vessel (see Plate 4.1). Plate 4.2 shows how the polymer looks when precipitated as cocoons in hexane. Table 4.1 summarizes the data on the various batches sent to SRI for spinning and gives data on some other batches made during the past year.

We have had problems with large batches because the polymerization reaction is quite exothermic and the viscosity of the resulting polymer is so high that even a 50% solution in benzene is too viscous to permit vaporization of the benzene and cooling by refluxing. The result is that the mass swells and overflows the vessel. Decreasing the ratio of monomer to benzene helped a great deal (lot 26341) and the overflow from this lot was much less than from previous large batches. A further dilution with benzene should improve matters still further.

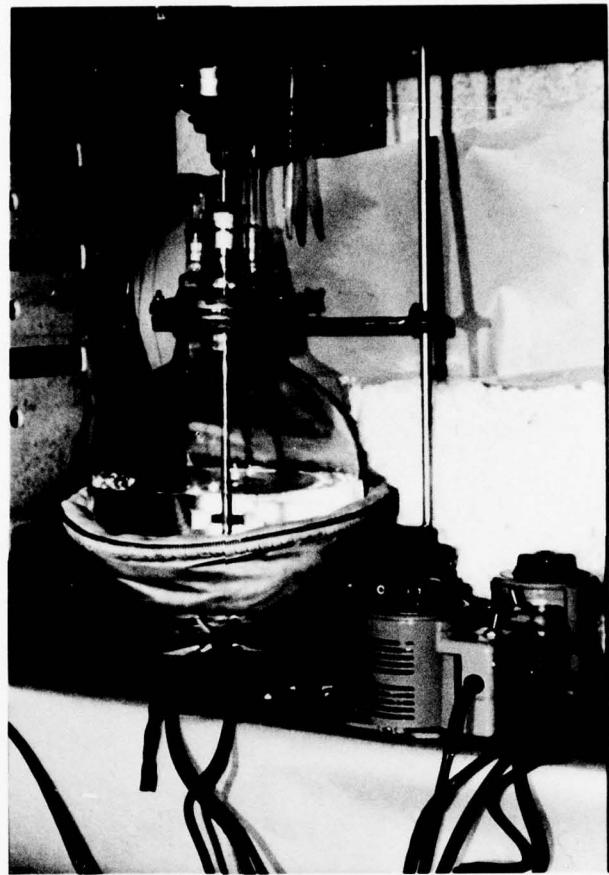


Plate 4.1. Large Scale Polymerization of Distilled 6-hexanolactone to Poly- ϵ -caprolactone.



Plate 4.2. Precipitation of Poly- ϵ -caprolactone in hexane. The White Material on the Rod is a so-called "Cocoon."

TABLE 4.1
SUMMARY OF ϵ -CAPROLACTONE POLYMERIZATIONS⁽¹⁾

Batch No.	Amount of ϵ -Caprolactone g	Catalyst % W/W	Amount Benzene g	Time (Hrs)	Molecular Weight M_w	Intrinsic Viscosity [n]
22397 ⁽²⁾	5537g (5160 mls)	.23 ⁽³⁾ (93 mls)	5448g (6190 mls)	20	118,000 97,000	1.44 1.22 ⁽⁴⁾
22397-1 ⁽⁴⁾						
26902	5537g (5160 mls)	.31 ⁽³⁾ (125 mls)	5448g (6190 mls)	24	76,000	1.00
26902-1 ⁽⁶⁾					56,000	.774 ⁽⁷⁾
26318 ⁽⁷⁾	537g (500 mls)	.23 ⁽⁸⁾ (9 mls)	528g (600 mls)	24	152,000	1.76
26321 ⁽⁹⁾	537g (500 mls)	.31 ⁽⁸⁾ (12 mls)	634g (720 mls)	24	105,000	1.30
26341 ⁽¹⁰⁾	4569g (4250 mls)	.13 ⁽⁸⁾ (45 mls)	5368g (6100 mls)	24	152,000	1.73

NOTES

- (1) See Appendix 4.1 for general procedure.
- (2) Several minutes after the addition of the catalyst, the temperature of the batch increased rapidly due to the heat of reaction. The heating mantles were turned off at this point. The batch became very viscous and hot enough to boil the benzene. The volume increase due to the bubbles of benzene vapor caused a portion of the material to overflow the 22 liter kettle. This batch was sent to SRI on 1/30/76 for spinning into Lot 1 of PCL fiber.
- (3) Diethyl benzene (DEZ) in benzene 15% by weight, density 0.91 (est.).
- (4) Approx. 1969 g of PCL lot 22397 was returned to Dynatech from SRI for filtration to remove foreign matter and reprecipitation. 1800 grms of the filtered PCL was sent back to SRI on 7/21/76 for spinning into Lot 2 of PCL fiber. This was labelled 22397-1. Note that [n] dropped to 1.22 from 1.44 as a result of the reprecipitation.
- (5) The polymerization reaction had not occurred 45 minutes following the injection of 95 mls of DEZ. 30 mls additional of DEZ from a new bottle was injected. Several minutes after the second injection the temperature of the system increased rapidly. Foaming and expansion began because of the vaporization of the benzene. The volume increase caused a portion of the material to overflow out of the 22L kettle.
- (6) Due to the appearance of foreign particles in the precipitated polymer, the PCL was filtered and reprecipitated. The batch was then called 26902-1. This material was sent to SRI on 10/14/76 for spinning into Lot 3 of PCL fiber. Note that the [n] dropped to .774 from 1.00 as a result of the reprecipitation.
- (7) Redistilled benzene was used in making this polymer. Approx. 10 minutes after the addition of the catalyst, the reaction temperature slowly began to rise. The mixture turned a slight yellow color. Approx. 20 minutes following the injection of catalyst, the mixture became more viscous with no further color change. At this point the reaction temperature substantially increased to a high point of 92°C and a pronounced yellow color developed. After 1 hr. the expansion of the mixture due to vaporization of the benzene ceased. There was no material overflow.
- (8) 14.4% DEZ in Toluene.
- (9) Redistilled benzene was used in making this polymer. There was no noticeable reaction 1 hour after the addition of 9 mls of DEZ catalyst. The only noticeable change was the development of a slight yellow color. 3 additional mls of DEZ were then added. Several minutes later, the reaction proceeded rapidly with noticeable expansion due to vaporization of the benzene and an increase in temperature to 84°C. Unlike previous batches, this polymerized mixture was sufficiently fluid to permit the benzene vapor bubbles to collapse when the temperature of the mixture dropped back to 60°C.
- (10) Redistilled benzene was used in making this polymer. A rise in temperature and thickening of the mixture began almost immediately following the addition of 45 mls of catalyst. The heating mantle was turned off but the temperature and viscosity continued to increase rapidly and the thermocouple broke at a reading of 70°C. Foaming and expansion began due to benzene vaporization. The volume increase caused a portion of the material to overflow out of the 22 liter kettle. However, the mixture soon cooled below the boiling point of benzene causing the foam to collapse so the overflow which was collected on release paper could be returned to the flask.

We also found that use of redistilled benzene appears to improve yields and permits use of less catalyst. In Batch 26341 we used only 0.13% catalyst whereas previously 0.22% had been thought to be the minimum which would give a reaction (Third Annual Report dated January 27, 1976, Dynatech Report No. 1363, page 10).

4.2 Melt Spinning

Melt spinning of PCL was performed at Southern Research Institute (SRI) under the direction of R.L. Meek and A.C. Tanquary. As delivered, the dried PCL cocoons were too fluffy for direct feeding into SRI's melt spinning extruder. Therefore it was necessary to compress and chop the material according to the following procedure.

1. Compress cocoons into sheets.
2. Cut sheets into chips.
3. Chill chips at 0°C to maximize crystallinity.
4. Grind chips with dry ice.
5. Thoroughly dry ground chips under vacuum.
6. Extrude the ground chips into rod at about 120°C using ice-water quench bath.
7. Chop rod into pellets.
8. Thoroughly dry pellets under vacuum.

The resulting pellets were readily accepted by the extruder.

The description of the melt spinning experiments taken from SRI's report to Dynatech follows.

Melt Spinning Experiments

Most of the melt spinning experiments were carried out on a 3/4-in. melt extruder equipped with a metering pump, a filter pack, and a spinneret. Three different filter packs were used. One pack contained 20-30-mesh sand, one contained 10-20-mesh sand, and the other contained 12-mesh glass beads. Two spinnerets were

used. One spinneret had 10-mil-diameter orifices and the other had 12-mil-diameter orifices. Both spinnerets had 68 orifices and 2:1 L/D ratio.

The yarns were vertically extruded and air cooled as they passed from the spinneret through an air quench chamber (5-ft. long) (See Plate 4.3) then a spinway stack (12-ft. long), then over twin take-up godets, and finally to a model 959R Leesona winder, where they were collected on paper tubes.

In preparation for the initial melt-spinning trial, the equipment was lined out with Union Carbide PCL-700 resin at a melt temperature of about 123°C and a feed rate of about 1-lb/hr. The pack pressure during the spinning of PCL-700 was about 1500 psig; however, when the Dynatech resin (first sample) was charged, the pack pressure immediately increased to 2700 psig and then gradually increased in about 1-1/4 hour to 5000 psig, which is our maximum safe operating pressure.

No difficulties except pressure build-up were encountered in the initial run at a take-up speed of 305 ft/min; however, the yarns (about 645 denier) were found to contain non-uniform filaments when observed microscopically.

In efforts to eliminate the pressure build-up problem, we used the ground but unpelletized polymer, and we tried decreasing rates, increasing temperatures, increasing orifice sizes, and using lower-resistance screen packs, all with no significant beneficial effects. In most attempts, 5000 psig was reached in less than an hour of operation.

Two runs were made with the pelletized polymer. In the first, a filter pack was used containing 20-30-mesh sand. The resin feed was about 0.6 lb/hr at 122°C, and 5000 psig was reached in a few minutes. Temperature was increased to 156°C, but the pressure re-

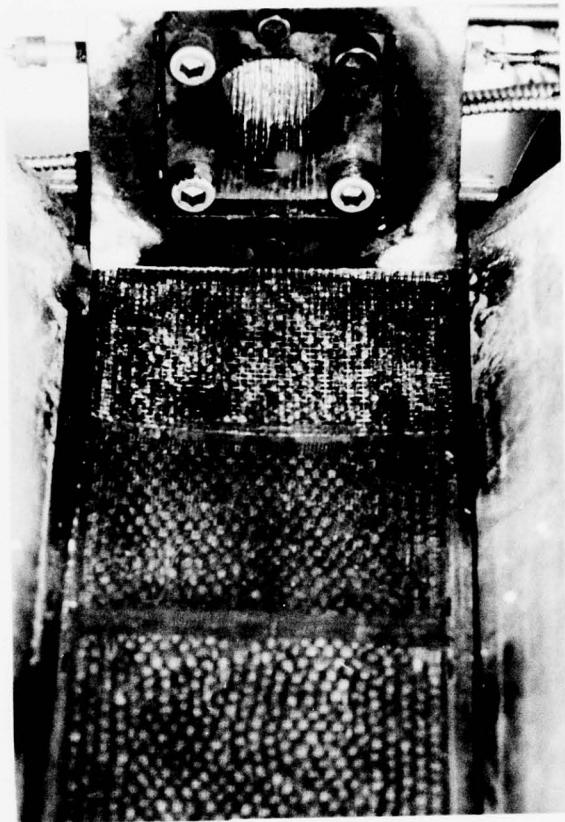


Plate 4.3. Poly- ϵ -caprolactone Coming out of 68 Orifice Spinneret and Passing through Air Quench Chamber. (SRI)

mained at 5000 psig. At this point, the spinneret which had 10-mil orifices was replaced with one having 12-mil orifices, the filter pack was changed to 12-mesh glass beads, and the melt temperature was increased to 164° C. The pressure decreased to 600 psig, but the fibers were too weak to be collected on the take-up equipment. The fibers contained entrapped particles but also appeared "mottled" under the microscope; their appearance suggested that the pellets had not been thoroughly dried.

Therefore, the pellets were dried for an additional 10 days under vacuum at 30° C. The final melt spinning test on the 3/4-inch extruder repeated the previous set-up and used a spinneret with 68 orifices 12-mils in diameter with a 12-mesh glass-bead filter pack. We started the test at a feed rate of about 0.7 lb/hr and a melt temperature of 186° C. We continued spinning efforts until the temperature had been incrementally decreased to 108° C. No satisfactory spinning conditions were found. The yarns were too weak to collect and contained entrapped particles over the entire temperature range investigated.

To define more precisely the causes of the difficulties in spinning the Dynatech resin, we spun a small quantity (about 10g) of the pellets on the ram extruder. The extruder was equipped with a spinneret having 7 orifices 12-mils in diameter and a filter pack composed of a 40- and a 250-mesh stainless steel screen.

In this experiment, the dried pellets were charged to the extruder preheated to 125° C. The resin was allowed 25 min to melt and reach equilibrium. The resin was then forced by a motor-driven ram (ram pressure of 670 psi) through the spinneret at a rate of 0.7 cm^3/min . The yarn was collected on a surface-driven winder at 20 ft/min.

No difficulties were encountered in spinning or collecting this yarn (about 930 denier) at this slow resin feed rate. How-

ever, the large filaments contained numerous entrapped particles which could cause breakage in smaller yarns spun at higher resin feed rates. Such particles have never been observed in fibers that have been spun from PCL-700.

Orienting Experiments

Portions of the yarns spun from the Dynatech resin and the yarns spun from Union Carbide PCL-700 were oriented on the draw winder. In most of these experiments the yarns were fed from the feed spool through tensioning devices to a feed godet, then drawn as they passed over a heated platen at 37°C to a second godet, and finally collected on a model 959R Leesona winder. (See Plate 4.4). The Dynatech yarns were drawn at a draw ratio of about 4.7X while the PCL-700 yarn was drawn at about 3.5X.

Some difficulties were encountered in drawing the yarns due to non-uniformity and also due to the static build-up on the yarn during drawing (no spin finish was applied during spinning). We were able to overcome the problem of static by installing static eliminators along the fiber line, drawing the yarns at slow speeds, and applying a mineral oil lubricant on the yarn between the draw godet and winder.

About one pound of the spun fiber designated Lot 1 was delivered to the Philadelphia College of Textiles and Science (PCTS) for knitting (See Section 4.3 below).

SRI encountered processing difficulties caused by an insoluble impurity in the polymer which caused excessive pressure build-up in the extruder and breakages in the spun filaments during orientation.

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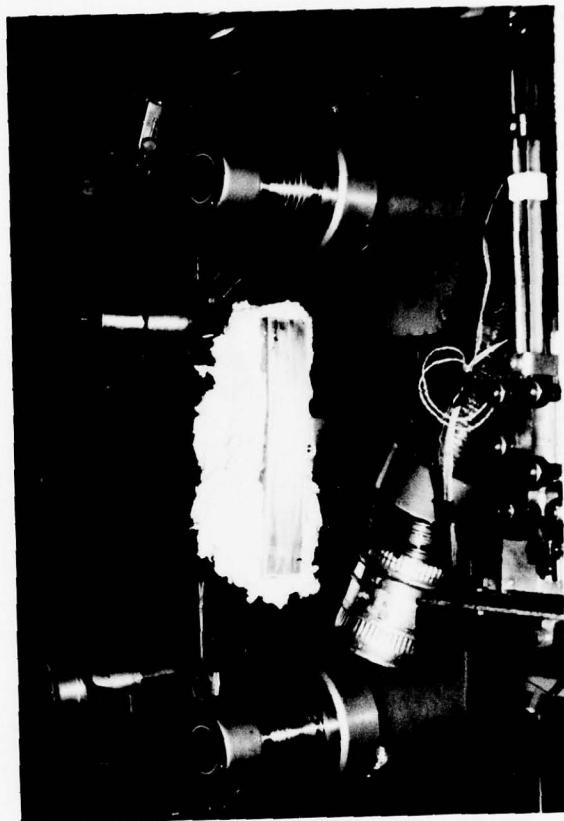


Figure 4.4. The yarn is drawn (oriented) as it passes from a Feed Godet over a Heated Platen to a Second Godet Operating at a Higher Speed than the First. (SRI)

The unused portion and the waste (4.5 lbs. left from the original 10 lbs.) of PCL number 26306 were returned to Dynatech (See Table 4.1). The material was redissolved, filtered to remove the impurity, and reprecipitated. The molecular weight of the reprecipitated material was 97,000 (See Table 4.1).

From the four pounds of reprecipitated material called PCL 26397-1 about 1.4 pounds of oriented 68 filament yarn was produced by SRI. The details of the procedure selected for this batch of fiber designated lot 2 are given in Appendix 4.2. The average denier of this fiber was 175. The tenacity was about 1.6g/f and the elongation at break 64%. The draw down was not uniform and microscopic examination showed fiber diameter to vary from 1 to 4 mils. Many of the fibers have short, thick sections 1/4" to 1/2" in length and some fibers are thick for long distances.

Seven pounds of PCL batch 26902-1 was sent to SRI for spinning. The yield of useable fiber from this lot called lot 3 was 3.4 pounds. The details of the procedure which was similar to that used previously except that it included twisting and sizing of the fiber is given in Appendix 4.3. The final twist after drawing was about 0.3 tpi. The yarn in lot 3 had an average denier of 173, a tenacity of 1.6g/d and an elongation at break of 80%.

4.3 Knitting

Although problems were encountered during melt spinning, one pound of useable, 120-140 denier yarn was made. The fiber was taken to the Philadelphia College of Textiles and Sciences where it was warp knitted under the director of Professor Thomas Edman. (Prior to knitting three twists per inch were put into the yarn.) The yarn was knitted such that upon "finishing" -- the process of brushing the surface to form a pile -- an open-looped velour/velveteen type surface resulted. Five pile depths were prepared. The knitted, finished fabrics were sent to Dynatech where they were laminated to PCL films.

The second lot of fiber was also taken to the Philadelphia College of Textiles and Science where it was then knitted under the direction of Professor Thomas Edman at Titone, Inc. in Burlington, New Jersey. Some of the fiber was knit into a velour similar to fabric number IV-22 described in Table 4.2 and some into a cut plush in which the pile is formed by individual fibers instead of loops. Both of these two fabrics used 56 denier Dacron for the backing because of the limited amount of PCL fiber. These two fabrics knitted from fiber lot 2 are to be evaluated during the coming year.

The use of cut plush instead of a looped velour should permit removal of the synthetic graft with less tearing of the underlying tissue.

A double needle bar Raschel machine was used to knit the plush fabric at Titone, Inc. There are three spools of yarn feeding this machine -- one feeding each needle bar and one the spool containing the PCL fiber feeding both bars alternately forming threads going from one fabric to the other (See Plate 4.5). The woven fabric is then cut in half through the crossing threads, creating two pieces of plush fabric.

4.4 Lamination of PCL Fabric to PCL Film

The details of the process used to laminate the PCL fabric knitted from lot 1 of fiber to PCL film are given in Appendix 4.4.

4.5 In Vivo Evaluation

Thirty-two PCL fabric PCL film laminates cut to approximately 2" x 3" were placed on full thickness excision wounds on the backs of 200-250 gram male Wistar rats and held in place using 9 mm stainless steel wound clips. Details of the grafting procedure are seen in Appendix 4.5. The grafting was carried out by J.F. Howes, Ph.D. at SISA, Inc., Cambridge, Mass. Three days after grafting the strength of the interfacial bond that had developed between the wound and the covering was measured at Dynatech using an Instron Model TT-C Tensile Tester. Prior to testing the adhesion,

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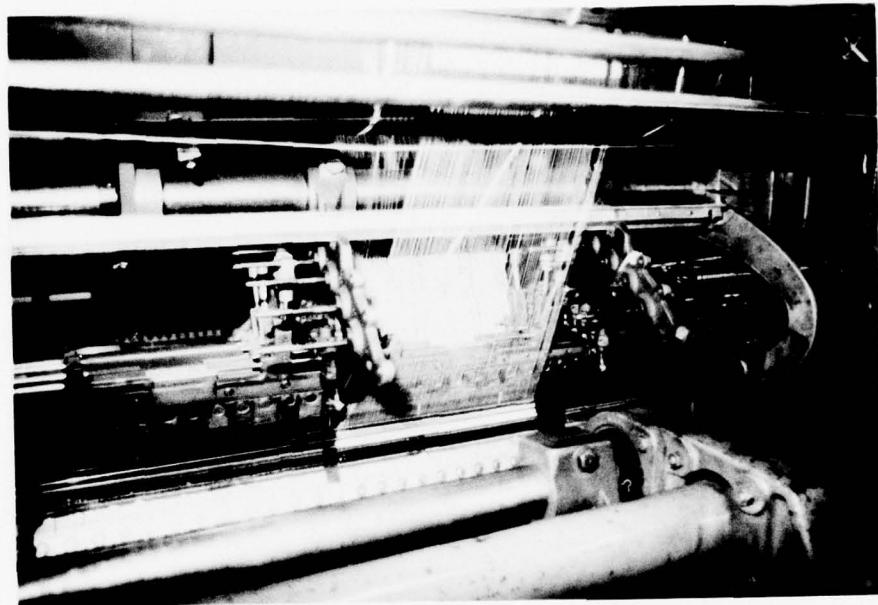


Plate 4.5. Front View of Raschel Double Bar Knitting Machine. Note three banks of fiber, one feeding back bar, one the front, and the center one feeding both.

the stainless steel wound clips were removed and the edges of the covering cut with scissors to produce an even width strip about 2" wide. The covering was removed at a rate of 3"/min (jaw separation 6"/min) in a posterior anterior direction. The description of the laminates and the results are summarized in Table 4.2.

There were two important findings:

- The degree of adhesion increased with the increase in amount of nap in the fabric. However, the amount of nap is critical with a very light nap appearing to be optimum. With heavier naps, the fabric adhered too well so that a considerable amount of the new tissue formed beneath the covering was torn from the back of the rat when the graft was removed three days after application.
- The PCL fabric PCL film laminates were thicker than the grafts used previously and were somewhat too stiff to conform to the compound curves required to conform to the back of an active rat without forming creases or puckers along the two edges of the graft. These creases permitted access of air, pockets of slight infection, and non-adherence.

The grafts were dry to the touch and other than the defects noted were well tolerated by most of the rats. No unusual inflammation was noted other than the occasional slight pockets of infection where the grafts did not adhere due to the creases.

4.6 Further Work on the Development of PCL Fabric Film Laminate Burn Coverings

Final preparation and evaluation of the poly- ϵ -caprolactone or fabric laminate burn covering will be carried out. The object of this task will be to complete development and deliver to NMRI a suitable covering material ready for testing on swine. Specific work that will be accomplished is as follows:

4.6.1 Complete Preparation of Selected Fabrics for Lamination

Polymer already synthesized on the present program will be spun into yarn and knitted or woven into selected fabrics for evaluation on rats.

4.6.2 Evaluation of Fabric/Laminate Burn Covering

Radioactively labelled proline will also be used in the evaluation of the fabric/laminate burn covering. The objective will be to obtain a quantitative measure of the fibrin ingrowth, especially during early stages of burn treatment. This quantitative measure of new cell growth into the burn covering, especially within the first 2-1/2 hours post-covering, will supplement the present adherence testing method.

4.6.3 Supply Samples and Coordinate Work with NMRI

With the final testing that is being carried out prior to clinical testing, it is essential to maintain close coordination between work at NMRI on swine and the burn covering testing and evaluation at Dynatech. Samples will be supplied to NMRI and results using this material on smaller animals and other tests will be well documented.

4.6.4 Evaluation of Burn Covering Materials in Anticipation of Clinical Trials

Standard sterilization procedures will be evaluated and tested on both the wipe-on and the fabric/laminate burn treatment systems. Radiation sterilization and ethylene oxide sterilization will be evaluated. Appropriate FDA staff will be contacted to determine potential requirements. Communications with FDA staff on other biomaterials development programs have proved to be valuable in anticipating regulatory requirements.

APPENDIX 4.1

POLYMERIZATION OF 6-HEXANOLACTONE. (ϵ -CAPROLACTONE)
TO POLY- ϵ -CAPROLACTONE

Appendix 4.1

POLYMERIZATION OF 6-HEXANOLACTONE (ϵ -CAPROLACTONE) TO POLY- ϵ -CAPROLACTONE

To obtain high molecular weight polymer suitable for fiber and film making, pure 6-hexanolactone is required as the reactant. As received from Eastman Chemical Co., 6-hexanolactone is slightly yellow and, therefore, it purified by vacuum distillation (15 mm Hg, 118°C) to a water-white liquid before use.

To a three-neck flask equipped with agitator, Dean-Stark trap, and condenser charge equal weights of distilled 6-hexanolactone (sp.g. 1.073) and benzene (sp.g. 0.88). Under nitrogen purge, heat to 60°C and hold at that temperature for one hour after the initiation of overflow from the Dean-Stark trap. Then add the catalyst. (Within 10 minutes a temperature rise accompanied by an increase in the viscosity will be observed.) Maintain at 60°C for the time specified. Cool. Dissolve polymer in benzene. Collect the polymer by precipitation in hexane. Dry polymer under vacuum at 45-50°C.

Determine the approximate intrinsic viscosity $[n]$ in benzene.
(Average of inherent and reduced viscosity of 0.2 g/dl in benzene at 37°C.)

$$M_w = \frac{0.82}{\sqrt{\frac{[n]}{9.94 \times 10^{-5}}}} \quad (\text{Reference 15})$$

APPENDIX 4.2

PREPARATION OF PCL FIBER LOT 2 MELT SPUN BY SRI

Appendix 4.2

PREPARATION OF PCL FIBER LOT 2 MELT SPUN BY SRI

Preparation of Resin for Melt Spinning

The 4-pound lot of resin 26306A received from Dynatech was in the form of fluffy "cocoons" too large to feed directly to the extruder of either the pelletizer or the melt spinning equipment. Therefore, the cocoons were converted into particles suitable for melt spinning as follows:

The fluffy cocoons were first pressed into irregular sheets about 1/8-in. thick with a two-roll rubber mill at room temperature. These sheets were then cut into chips about 1/2-in. square with a paper cutter. The chips were then mixed with ice (to obtain maximum resin crystallinity at 0°C) and allowed to stand for 1/2-hour. They were drained, mixed with dry ice (to remove heat during milling), and ground in a Wiley mill through a 1/4-in. diameter screen. The ground chips were dried for 7 days in a vacuum oven at 30°C.

The dried chips were then pelletized on a 1-in. Killion extruder equipped with a nylon-type screw, a screen filter pack (two 40-mesh S.S. screens), and a 1/8-in. rod die. The temperatures in the extruder were between 88°C and 94°C. The resin required hand feeding but was extruded at about 2-1/2 lb./hr. into a 10-ft-long ice-water bath, then through pressure type take-up rolls into a Wiley mill for grinding into pellets (about 1/8-in. x 1/8-in.). The pellets were then dried for 6 days in a vacuum oven at 30°C. During the pelletization and before the molten polymer was quenched, a few unmelted particles were observed in the extrudate.

Melt Spinning Experiments

The dried pellets were melt spun on a 3/4-in. melt extruder equipped with a metering pump, a filter pack, and a spinneret. The filter pack contained a 40-mesh and a 250-mesh stainless steel screen and 20-30

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mesh Ottawa sand. Two spinnerets having 68 orifices 12 mils in diameter were used. One had a 2:1 L/D ratio and the other had a 4:1 L/D ratio. The yarns were vertically extruded and air cooled as they passed from the spinneret through an air quench chamber (5-ft-long), then a spinning stack (12-ft-long), then over twin take-up godets, and finally to a model 959R Leesona winder, where they were collected on paper tubes.

In this experiment the caprolactone pellets were charged to a "clean" extruder and the temperatures of the extruder adjusted to give a uniform polymer flow (177°C melt temperature). The spinneret having 68 orifices 12 mils in diameter and 24 mils long (2:1 L/D) was installed, and the extruder temperatures and polymer feed rate were adjusted until satisfactory conditions were established for collecting the yarn. As one of the spinneret orifices had fouled while establishing conditions, a clean spinneret which had 68 orifices 12 mils in diameter and 48 mils long (4:1 L/D) was substituted and the yarns collected for orienting. The polymer feed rate was about 1 lb/hr; the melt temperature was 144°C; the pack pressure was 2700 to 3100 psig; and the yarn take-up speed was 189 ft/min.

The yarns spun well under these conditions, but after spinning the unoriented yarn contained an occasional filament break and also appeared to be non-uniform along the length of the yarn.

Orienting Yarns

The yarns were oriented on a draw winder as follows: The yarns were fed from the feed spool through tensioning devices to a feed godet, then drawn 5.3X as they passed over a heated platen at 37°C to a second godet, and finally collected on a model 959R Leesona winder. A static eliminator was located about 1 in. from the fiber line between the winder and the feed godet.

Some difficulties were encountered in drawing the yarns due to non-uniformity and broken filaments. No major difficulties with static build-up were encountered on the yarns; therefore, no spin finish was applied to the yarn.

APPENDIX 4.3

PREPARATION OF PCL FIBER LOT 3 MELT SPUN BY SRI

Appendix 4.3

PREPARATION OF PCL FIBER LOT 3 MELT SPUN BY SRI

Preparation of Resin for Melt Spinning

The 7-lb lot of resin number 26902-1 in the form of fluffy "cocoons" was first pressed into irregular sheets about 1/8-in. thick with a two-roll mill at room temperature. The sheets were then cut into chips about 1/2-in. square with a paper cutter. The chips were enclosed in polyethylene bags and the bags and contents were packed in ice and stored for 24 hours. Note that in previous procedures the chips were mixed directly with the ice. The chips were then mixed with dry ice and ground in a Wiley mill through a 1/4-in.-diameter screen. The ground chips were dried for 5 days in a vacuum oven at 30°C.

The dried chips were pelletized on a 1-in. Killion extruder equipped with a nylon-type screw, a screen filter pack (two 40-mesh s.s. screens), and a 1/8-in. rod die. The temperatures in the extruder were about 94°C in the extruder feed zone, 110°C in the extruder metering zone, and 92°C in the die. The resin required hand feeding but was extruded at about 2-1/4 lb/hr into a 10-ft-long ice-water bath, then through pressure-type take-up rolls into a Wiley mill for cutting into pellets (about 1/8-in. x 1/8-in.). The pellets were dried 4 days in a vacuum oven at 30°C. During the pelletization and before the molten polymer was quenched, a few unmelted particles were observed in the extrudate.

Melt Spinning Experiments

The dried pellets were melt spun on a 3/4-in. melt extruder equipped with a metering pump, a filter pack, and a spinneret. The filter pack contained a 40-mesh and a 250-mesh stainless steel screen and 20 to 30-mesh Ottawa sand. A spinneret having 68 orifices 12 mils in diameter was used. The yarns were vertically extruded and air cooled as they passed from the spinneret through an air quench chamber (5-ft long), through a spinning stack (12-ft long), over twin godets, and finally to a Model 959R

Leesona winder, where they were collected on paper tubes.

In the experiment in which the yarns for orienting were produced (Experiment 8095-113), the caprolactone pellets were charged to the extruder, and the temperatures of the extruder were adjusted to give a uniform flow (initial temperature of 169°C). The spinneret assembly was installed and the polymer feed rate and extruder temperatures adjusted until satisfactory conditions were established for collecting the yarn. The most satisfactory conditions investigated were with a polymer feed rate of about 1 lb/hr and a melt temperature of 153°C. The pack pressure at these conditions was 1250 to 1500 psig. The yarn take-up speed was about 222 ft/min.

Although a considerable quantity of resin was spent while spinning conditions were being established, this resin spun the most satisfactorily of any lot to date and the yarns appeared to be the most uniform of any lot. After spinning, however, the unoriented yarn had low strength and contained some broken filaments.

Orienting Yarns

The yarns were oriented on a draw winder as follows: The yarns were fed from the feed spool through tensioning devices to a feed godet, then drawn 4.5 to 4.9X as they passed over a heated platen at about 46°C to a second godet, and finally collected on a Model 959R Leesona winder at 45-50 ft/min. A static eliminator was located about 1 in. from the fiber line between the winder and the feed godet.

About 1.5 tpi was added to the yarn before orienting by rotating the yarn feed spool as the yarn was fed to the first godet (final twist of about 0.3 tpi). A small amount of lubricant solution consisting of 10% of Drakeol 35 mineral oil (Penreco, Inc.) in hexane was also applied to the oriented yarn with a wick applicator located between the second godet and the winder.

This lot of yarn appeared to draw more uniformly and with fewer difficulties than either of the previous lots, but some difficulties were encountered in orienting due to the broken filaments and the low strength of the feed yarn.

APPENDIX 4.4

PREPARATION OF PCL FABRIC PCL FILM LAMINATES

Appendix 4.4

PREPARATION OF PCL FABRIC PCL FILM LAMINATES

10 grams of PCL polymer 22397, intrinsic viscosity 1.15, was dissolved in 100 mls of tetrahydrofuran (THF) and filtered through a 25μ Teflon Millipore filter. A glass plate was sprayed with Frekote 33 (Frekote, Inc.), wiped thoroughly and polished with a clean paper towel. A film of the PCL polymer solution was then cast onto the plate using a Boston Bradley Blade set at 25 mils and allowed to dry for 4 mins \pm 0.1 min. The non-napped side of the PCL fabric was then gently pressed against the film. The laminate was then peeled from the plate and the residual THF allowed to evaporate from the laminate.

APPENDIX 4.5

DESCRIPTION OF THE BURNED RAT MODEL
EXCISION AND GRAFTING PROCEDURES

Appendix 4.5

DESCRIPTION OF THE BURNED RAT MODEL EXCISION AND GRAFTING PROCEDURES

Poly- ϵ -caprolactone fabric film laminates obtained from Dynatech R/D Company were evaluated for adherence to full thickness excision wounds as follows. Male Wistar rats weighing between 200 and 250 grams were anesthetized by an intraperitoneal injection of sodium pentobarbital (40 mg/kg), and shaved with a #40 blade electric clipper. Twenty percent of the rat's skin was excised from the dorsal surface using clean technique and sterile instruments, and one of the laminates measuring approximately 2" x 3", was placed on the open wound. No attempt was made to prepare the wound prior to excision or application of the covering which was clipped in place with 9 mm wound clips. Post excision and grafting, each rat was kept in an individual cage in an unsegregated room and given food and water ad libitum. Room temperature and humidity were kept constant.

APPENDIX A

U.S. Patent #3,935,308 (Jan. 27, 1976), "Wound Covering
and Method of Application

DYNATECH R/D COMPANY TEL. 617-868-8050
99 ERIE STREET • CAMBRIDGE, MA 02139 • USA



November 17, 1976

Dr. Kenneth W. Sell
Commanding Officer
Naval Medical Research Institute
National Naval Medical Center
Bethesda, Maryland 20014

Dear Dr. Sell:

I'm sure you will be pleased to learn of the issuing of a patent on our burn covering program -- a copy is enclosed for your review. I believe this applies to our wipe-on type system. I understand from Mr. Robert Adams of the patent group of ONR that the Navy, after a detailed patent search, has decided to apply for two additional patents -- these are for the freeze-dried foam/laminate and the freeze-dried collagen/laminate. The Navy had decided not to apply for a patent on the dried collagen/polymer laminate. I recently sent in to the Navy a draft of a disclosure on the fabric/laminate -- Mr. Adams believes the Navy will attempt to obtain a patent on this system.

As with the enclosed patent, the inventors on all disclosures are Schwope, Wise, and Sell -- I added Mr. Gregory's name to the fabric/laminate write-up.

Sincerely yours,

D.L. Wise, Ph.D.
Manager, Biochemical Engineering

DLW/eah
Enclosure
cc: Dr. Bond
Dr. Callahan

United States Patent [191]
Wise et al.

[11] 3,935,308
[45] Jan. 27, 1976

[54] WOUND COVERING AND METHOD OF
APPLICATION
[75] Inventor Donald L. Wise, Belmont; Arthur D.
Schwartz, Watertown, both of Mass.;
Kenneth W. Sell, Rockville, Md.
[73] Assignee The United States of America as
represented by the Secretary of the
Navy, Washington, D.C.
[22] Filed Aug. 8, 1974
[21] Appl. No. 495,705
[52] U.S. Cl. 424/78; 424/45; 424/DIG. 13
[51] Int. Cl. A61K 31/74
[58] Field of Search 424/DIG. 13, 45, 78
[56] References Cited
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Chemical Abstracts, Vol. vol 78, (1969), 123181.

Primary Examiner—Frederick E. Waddell
Attorney, Agent, or Firm—Richard S. Schaefer; Don D.
Doty; Harvey A. David

[57] ABSTRACT

A preparation and a method are described for emergency, interim treatment of extensive burn injuries, e.g., flash burns, to external portions of a person. A solution of the polymer poly-*ε*-caprolactone in a volatile solvent, such as acetone or tetrahydrofuran, is applied to the burn area by spraying or swabbing, so that upon evaporation of the solvent a film of the polymer is left to serve as a barrier to insensible water loss.

1 Claim, No Drawings

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WOUND COVERING AND METHOD OF APPLICATION**STATEMENT OF GOVERNMENT INTEREST**

The invention described herein may be manufactured and used by or for the Government of the United States of America for Governmental purposes without the payment of any royalties thereon or therefor.

FIELD OF THE INVENTION

This invention relates to the treatment of burn wounds, and more particularly to a method and means for providing such treatment as a "first aid" expedient, and at times as part of more sophisticated supportive treatment.

Shock is a major cause of death in the immediate period following a severe burn, such as a flash burn, over large portions of the body. A primary cause of shock has been recognized as the excessive loss of body fluids and protein through the burned areas. This loss occurs primarily through evaporation, and the process is not visible or otherwise readily detectable to the subject or observer. The loss is therefore termed inensible, although the results thereof are dramatically apparent in the shock process.

Many, if not most, burn accidents occur under circumstances that make it impossible for the victim to receive immediate supportive treatment in a hospital. Such is the case, for example, with disasters, accidents, or conflicts occurring in remote areas, at sea, or under other adverse conditions. Accordingly, there has long been a need for suitable, adequate, readily available, and easily applied burn treatment that can be administered by relatively unskilled persons at the scene of injury.

DISCUSSION OF THE PRIOR ART

In the past there have been used various creams, 40 greases, sprays, and homemade concoctions designed to sooth and protect the wound, immediately following a burn, as a first-aid treatment. In general, these have been ineffective in stopping inensible fluid and protein loss through the burn site and have been messy and 45 difficult to apply. The latter factors are, of course, deterrents to effective use by unskilled persons in a first-aid situation.

In addition, there have existed various coverings for burns and similar wounds requiring covering of a substantial area for extended periods of time during the skin regeneration and healing process. These have included skin grafts where the skin was obtained either from another person or animal, or from another area of the injured party. Also, there have been provided various sheets, foils, and webs or fabrics made from various synthetic plastic materials, animal collagen, and the like. Examples of the latter are described in U.S. Pat. No. 3,491,760 to Bernhard Braun et al. Use of burn wound coverings in the form of fibrillar products comprising polyglycolic acid are alluded to in U.S. Pat. No. 3,739,773 to Edard E. Schmitt et al. Those burn wound coverings, and particularly those comprising foams, gels or foils of collagen, or other moist, conformable dressing, require special storage techniques and facilities that render them quite impractical to have available for immediate use as a first-aid supply in various remote, isolated, and limited facility places where flash

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burns and other extensive injuries to the skin may occur.

SUMMARY OF THE INVENTION

5 The present invention aims to overcome some or many of the disadvantages and shortcomings of the prior art, with respect to emergency or first-aid burn dressings or treatment, through the utilization of our discovery that a thin plastic film of poly- ϵ -caprolactone formed directly on the surface of a burn wound will adhere thereto and will control inensible fluid loss by evaporation so as to occur at a substantially normal rate, and that such a film can be effectively formed by applying a solution of poly- ϵ -caprolactone in a suitable solvent, such as acetone or tetrahydrofuran.

10 With the foregoing in mind, it is a principal object of the invention to provide an improved wound covering which is suitable for first-aid use on burns, is sufficiently compatible with human tissues and fluids to adhere to a burn wound for a useful period of time, and is notably effective in maintaining fluid balance in a subject.

15 Another object of the invention is to provide a burn wound treatment materials which can be stored for prolonged periods of time in a convenient and readily usable form, without any requirement for special storage facilities or conditions.

20 Still another object is the provision of burn treatment material of the foregoing character and comprising poly- ϵ -caprolactone in a solvent or vehicle that will rapidly evaporate after application to a wound surface to leave a thin, covering film of the poly- ϵ -caprolactone adhering to the wound.

25 As another object, the invention contemplates the packaging of the poly- ϵ -caprolactone and its solvent in a container having means for ejecting the contents thereof in the form of a spray or aerosol onto an affected area to be treated, such as a flash burn.

30 Yet another object of the invention is to provide a method of burn treatment including the steps of forming a solution of poly- ϵ -caprolactone in a volatile solvent, applying a layer of the solution over a surface to be treated, and allowing the solvent to evaporate so as to form a film of poly- ϵ -caprolactone having a thickness in a predetermined range.

35 The poly- ϵ -caprolactone, with which the discovery of this invention is concerned, is a biodegradable solid polymer having a molecular weight in the range of 2,000 to 300,000, and which polymer is soluble in liquid solvents, specifically acetone and tetrahydrofuran. U.S. Pat. No. 3,021,309 to E. F. Cox et al describes the polymer poly- ϵ -caprolactone and its generation. The chemical derivation of the polymer per se is not 40 considered to be part of this invention, poly- ϵ -caprolactone having been known in the chemical arts for many years now, as is evident from that patent. Moreover, as 45 also pointed out by that patent, the polymer concerned is soluble in acetone, and is capable of being formed into films.

50 What is considered to be a notable advancement in the medical art is our discovery that a solution of poly- ϵ -caprolactone in a volatile solvent can be applied directly to a burn wound surface, and that the solvent will 55 evaporate to leave a thin, flexible film or skin of poly- ϵ -caprolactone that will adhere to the wound surface and will effectively control the evaporative water loss from a severe burn during the immediate post burn period.

and until more conventional supportive burn treatment can be undertaken.

DESCRIPTION OF THE PREFERRED EMBODIMENT

In carrying out the invention it is preferred that the solution of poly- ϵ -caprolactone be prepared with a solvent that is volatile and substantially non-irritating to a subject when applied thereto. Accordingly, in an exemplary embodiment the solvent may comprise the liquid acetone, and the prepared solution may be placed in a suitable container for prolonged storage in contemplation of possible future emergency use.

In some instances, it may be desirable to utilize a container that has spraying capability, such as the conventional aerosol spray can. A suitable propellant, such as that sold under the name Freon, may be included in a pressurized state in the container to facilitate spraying of the solution. Alternatively, the solution may be stored in a container without spraying capability, with the intention of applying the solution to a burn by means of a swab.

When an injury occurs that removes or destroys the normal water retaining capabilities of a subject's keratinaceous tissue, for example in the case of a severe abrasion, flash burn, or the like, the poly- ϵ -caprolactone and solvent solution is applied, either by spraying or swabbing, as a coating over the entire in-

jured area. As the solvent evaporates a thin flexible film of the polymer is left adhered to the wound surface. This film, which is preferably in the thickness range of about 0.0005 inch to 0.01 inch in thickness, replaces the destroyed natural keratin moisture barrier. Once the victim reaches a burn treatment center, the film can be removed and traditional burn treatment begins.

Obviously, other embodiments and modifications of the subject invention will readily come to the mind of one skilled in the art having the benefit of the teachings presented in the foregoing description. It is, therefore, to be understood that this invention is not to be limited thereto and that said modifications and embodiments are intended to be included within the scope of the appended claims.

What is claimed is:

1. A method of treating an extensive burn injury to an external portion of a person, comprising the steps of: spraying a layer of a solution of poly- ϵ -caprolactone, having a molecular weight in the range of 2,000 to 300,000, in a volatile solvent comprising liquid tetrahydrofuran onto said external portion; allowing said solvent to evaporate so as to leave a thin, flexible film of said poly- ϵ -caprolactone, having a thickness of about 0.0005 inch to 0.01 inch, adhering to said portion so as to form a barrier to body fluid loss therethrough.

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DYNATECH R/D COMPANY TEL. 617-868-8050
99 ERIE STREET • CAMBRIDGE, MA 02139 • USA